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Anthropometrics, physical activity, related medical conditions, and the risk of non-Hodgkin lymphoma

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Abstract

Background: Recent reports suggest that obesity, or conditions associated with obesity, might be risk factors for non-Hodgkin lymphoma (NHL), a cancer with dramatically increasing incidence in western countries over the last several decades. Physical inactivity increases the risk of obesity and of type 2 diabetes, but there are few data on the association of physical activity with risk of NHL.
Methods: We evaluated these factors in a population-based case–control study conducted in Detroit, Iowa, Los Angeles, and Seattle from 1998 to 2000. Incident HIV-negative NHL cases aged 20–74 years were rapidly reported in each area (n = 1321). Controls were identified through random digit dialing and Medicare files, and were frequency matched to cases on sex, age, race, and study site (n = 1057). Risk factor data were collected by in-person interviews and self-administered questionnaires. Unconditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (CI), adjusted for age, sex, race and study center.
Results: High body mass index (OR = 1.73 for 35+ *versus* < 25 kg/m^2; 95% CI 1.15–2.59) and history of gallstones (OR = 1.95, 95% CI 1.11–3.40) were positively associated with diffuse NHL, but were not associated with follicular or all NHL combined. Height was positively associated with risk of all NHL combined (OR = 1.38 for >70 *versus* <65 inches; 95% CI 0.98–1.94), and positive associations were apparent for both diffuse and follicular NHL. Non-occupational physical activity was inversely associated with risk of all NHL combined (ORs with increasing level: 1, 0.75, 0.71, 0.55, 0.68; *p*-trend = 0.04) and for diffuse and follicular NHL. We observed no association of total energy intake, type 2 diabetes, or hypertension with risk of NHL. In a multivariable model to predict risk of diffuse NHL, BMI (OR = 2.15 for 35+ *versus* < 25 kg/m^2; 95% CI 1.09–4.25) and height (OR = 1.63 for 71+ *versus* < 65 inches; 95% CI 0.75–3.57) were positively associated with risk while physical activity was weakly and inversely associated risk (ORs with increasing level: 1, 0.76, 0.72, 0.78, 0.82; *p*-trend = 0.9).
Conclusion: BMI and history of gallstones were positively associated with risk of diffuse NHL, supporting a role for obesity in this NHL subtype. Height was positively associated with NHL risk across subtypes, and suggests a role for early life nutrition in NHL risk. Non-occupational physical activity was only weakly and inversely associated with NHL risk after adjustment for obesity, height and alcohol use.

Introduction

In 2004, the American Cancer Society estimated that 54,370 persons will be diagnosed with non-Hodgkin lymphoma (NHL), and 19,410 will die from it [1]. NHL is now the sixth most commonly diagnosed cancer among both men and women. The incidence of NHL in the

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United States increased 3.3% per year from 1973 to 1990, a percentage increase exceeded only by melanoma of the skin, prostate cancer, and liver and intrahepatic cancer [2]. High rates of increase have continued since 1990 among women, but there has been a dramatic decline in rates among younger men (reflecting changes in the AIDS epidemic) and a slowing of the rate of increase among older men [3]. The increases among women and older men have been part of a longer trend evident since 1950 [4]. Improved medical technology, changing systems of diagnostic classification, known risk factors and the HIV epidemic can explain only a small part of this increase, leaving a majority of the increase unexplained [5].

Obesity and physical inactivity appear to play an important role in the etiology of several forms of cancer [6, 7]. The relatively limited data on obesity and NHL incidence or mortality have been mixed, with some studies reporting positive associations [8–11], but most reporting no association [12–19]. However, only a few studies had a reasonably large number (>250) of cases [8, 10, 11, 17, 19], were able to address potential confounding [8, 10, 11, 16, 17, 19], or assessed etiologic heterogeneity by NHL subtype [17, 19, 20]. Furthermore, obesity is a function of both energy intake and expenditure, but only two studies have simultaneously evaluated the role of obesity and NHL after accounting for caloric intake and physical activity [11, 17]. Obesity has cardiovascular effects (including increased risk of hypertension) and is a risk factor for type 2 diabetes, and the latter has been suggested as an NHL risk factor in some [21–28] but not all [29–33] studies. Physical inactivity is also a strong risk factor for all of these conditions [7]. Finally, adult height in part reflects the influence of nutritional factors during early childhood and adolescence on growth, with taller height reflecting more adequate (or excess) availability of food and energy and greater exposure to growth related hormones [34]. Height has been suggested as an NHL risk factor in some [16, 35] but not all studies [15, 17].

Given the importance and inter-related nature of these factors, we evaluated the association of anthropometric measures, caloric intake, physical activity, and related medical conditions with risk of NHL overall and for the two most common subtypes (diffuse and follicular NHL) in a population-based case–control study.

Methods

Full details of the study have been recently published [36, 37]. This study was reviewed and approved by human subjects review boards at each study site.

Case selection

We conducted this study in four areas with Surveillance, Epidemiology, and End Results (SEER) cancer registries [38]: the Detroit metropolitan area; northwestern Washington state; the state of Iowa; and Los Angeles County. Residents of these geographic areas who were aged 20 to 74 years (inclusive) and had a first primary diagnosis of NHL from 1 July 1998 through 30 June 2000 were reported to study personnel using a rapid identification and reporting system at each registry (developed to reduce losses to follow-up through illness and death). In Iowa and Seattle, all consecutive cases were eligible, while in Los Angeles and Detroit all African-American cases were eligible, but only a random sample of non-African-American cases were selected. HIV-positive cases were excluded. All cases were histologically confirmed, and cases were coded at each SEER registry according to the International Classification of Diseases – Oncology, 2nd Edition [39]. For this report, we evaluated all NHL and follicular and diffuse subtypes, as coded by the SEER program without central review.

Once identified, letters were sent to the patient's physician explaining the study and eligibility criteria. Of 2248 eligible cases, 320 (14%) died before we could conduct an interview, 127 (6%) could not be located, 16 (1%) had moved out of the area, and 57 (3%) had physician refusals. We attempted to contact the remaining 1728, but 274 (16%) declined to be interviewed, and 133 (8%) never responded or were not interviewed because of illness, impairment or other reasons. This left 1321 eligible cases who were enrolled into the study, for a participation rate of 76% of the cases that we attempted to contact, and an overall response rate of 59% of the living and deceased cases presumed to be eligible. Approximately 60% of the cases were interviewed within six months of their diagnosis, and 84% were interviewed within one year of their diagnosis. Response rates were highest in Iowa (68%), among women (62%), among white subjects (77%) and at ages 45–54 (64%). Response rates were also higher for patients with follicular (67%) than diffuse (51%) NHL.

Control selection

Population-based controls were selected from area residents aged 20 to 74 years (inclusive), and were frequency matched to the case age and sex distribution. Controls with a prior history of NHL or HIV infection were excluded. To select controls under age 65 years, we used one-step list-assisted random digit dialing [40]. In total, 42,640 telephone numbers were dialed over three

waves, and 78.5% of contacts provided a roster consisting of name, age, sex and race (for Detroit and Los Angeles) of each household member. Controls were then selected at random from these household rosters, stratified on geographic area, sex, age and race. Controls aged 65 to 74 years were randomly selected from Center for Medicare and Medicaid Services files of residents eligible for Medicare, also stratified on geographic area, sex, age and race.

Of the 2409 controls selected, 28 (1%) died before contact, 311 (13%) could not be located, and 24 (1%) had moved out of the geographic area. We attempted to contact a total of 2046, but 839 (41%) declined to be interviewed and 150 (6%) never completed an interview because of illness, impairment or other reason. Thus, a total of 1057 eligible controls were interviewed, for a participation rate of 52% of the controls that we attempted to contact, and a response rate of 44% of all presumed eligible controls. Control response rates were highest in Iowa (58%), among white subjects (54%), and at ages 55–64 (49%).

Data collection

We obtained written informed consent from each participant prior to interview. To accommodate a large number of questions, we used a split-sample design, with a core set of questions given to all respondents and the remainder given to participants in either Group A (all African-American and 50% of non-African-American participants) or Group B (50% of non-African-American participants). Prior to the in-person interview, participants were mailed a form for listing residential and job history, and either a family medical history questionnaire (Group A) or a diet and lifestyle questionnaire (Group B). During the interview, the interviewer administered a computer-assisted personal interview (CAPI) that included demographics, height and weight, occupational history, pesticide exposure and hair dye use. The Group A CAPI also included an extended medical history and use of illicit drugs, while the Group B CAPI also included an abbreviated medical history, cell phone use and sun exposure.

The self-administered diet and lifestyle questionnaire included a modified Block 1995 Health Habits and History Questionnaire [41, 42], a brief smoking history, and four questions on physical activity. Total energy (kcal/day) was estimated from the Block database. For the physical activity questions, participants were asked to report activities prior to one year, and included one question on occupational physical activity (''which characterized your time at work – mostly sitting with little walking; mostly walking with some sitting; mostly walking with some manual labor or exercise; mostly manual labor or exercise''); one question on household activity (''the work you did around the house, in the yard, and caring for your family, did you spend at least 30 min per day in vigorous activities that increased your breathing and heart rate above resting levels, such as working in the yard, heavy housework, or other manual labor?''); one question on moderate physical activity (''did you participate in moderate physical activity through sports or exercise, such as brisk walking''); and one question on vigorous physical activity (''did you participate in vigorous physical activity through sports or exercise that increased your breathing or heart rate to very high levels, enough to break a sweat?''). For the moderate and vigorous physical activity questions, participants were asked to report the number of days per week they participated in moderate (or vigorous) activities and approximately how long each session lasted.

Data analysis

We excluded missing (94 cases and 74 controls) and implausible (eight cases and six controls) anthropometric data. Height and weight were categorized according to quartile cutpoints in the control group. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and was *a priori* categorized as follows: <25.0 kg/m^2, 25.0–29.9 kg/m^2, 30–34.9 kg/m^2, and $35.0+$ kg/m^2. In secondary analysis, we categorized BMI according to quartile cutpoints among the controls. Medical conditions were categorized into response categories on the questionnaire. Type 2 diabetes was defined as diabetes with an onset after age 30 years. Physical activity was categorized either into the questionnaire response categories, or for continuous responses (frequency, duration), into categories based on the tertile cutpoints among controls. We also created a summary variable of total non-occupational physical activity in metabolic equivalents of energy expenditure (METS) per week, which was defined using lower limits provided by Centers for Disease Control and Prevention [43] as follows: the minutes of vigorous activity per week multiplied by six plus the number of minutes of moderate activity multiplied by three plus 270 if the participant engaged in vigorous house or yard work.

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of the exposure variables of interest with risk of NHL. For analyses of diffuse and follicular NHL subtypes, we used polychotomous logistic regression [44]. In regression models, we adjusted for the design variables of geographic location, age (in decades), sex and race (White *versus* non-White). For height,

weight, BMI and non-occupational physical activity, we evaluated whether there was a non-linear association with NHL risk by fitting smoothing splines with four degrees of freedom [45]. We also evaluated the potential confounding by educational level, family history of lymphoma, cigarette smoking, and alcohol use. A variable was considered a confounder if it changed the point estimates by greater than 10%. To assess the potential impact of our response rates on our associations, we evaluated the consistency of the main associations among subgroups in our data with differing response rates, including sex, age (20–59 *versus* 60–70 years), education (<16 *versus* 16+ years), study center, and race (as feasible). Statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC) and Splus (Mathsoft Inc, Seattle, WA).

Results

Table 1 summarizes the characteristics of this sample by case and control status and study group. Overall, cases were slightly younger (56.4 *versus* 58.1 years) and slightly more likely to be white (85% *versus* 80%) compared to controls, but the groups were reasonably balanced on age, sex, study center, and education. While we collected anthropometric data on all respondents, data on obesity-related medical conditions was only collected on Group A participants, and data on diet and physical activity was only collected on Group B participants. Respondents known in advance to be African-Americans were assigned to Group A, but a very small number who initially had unknown race were enrolled in Group B. The cases and controls in Groups A and B were similar with respect to sex and education, but Group B controls were somewhat older than Group B cases (59.7 *versus* 56.1 years).

Anthropometrics

Height was modestly and positively associated with NHL risk (OR = 1.38 for the tallest group; 95% CI 0.98–1.94; p-trend = 0.06) in the full sample (Table 2). We observed no clear associations of weight or BMI

Table 1. Descriptive characteristics by Group (Overall, A, B), SEER-NCI study, 1998–2000

Variable	All participants		Group A participants		Group B participants	
	Controls (n = 1057)	Cases (n = 1321)	Controls (n = 589)	Cases (n = 759)	Controls (n = 468)	Cases (n = 562)
Mean ± SD						
Age	58.1 ± 12.4	56.4 ± 12.6	56.9 ± 12.7	56.6 ± 12.4	59.7 ± 11.7	56.1 ± 12.9
Height (inches)	67.2 ± 4.0	67.6 ± 4.0	67.2 ± 4.1	67.6 ± 4.1	67.2 ± 3.9	67.6 ± 3.9
Weight (pounds)	177 ± 39	178 ± 38	178 ± 40	180 ± 39	174 ± 36	175 ± 38
BMI (kg/m^2)	27.4 ± 5.3	27.4 ± 5.4	27.7 ± 5.5	27.7 ± 5.4	27.0 ± 5.1	27.0 ± 5.4
Percent distribution						
Age						
20–64	58	67	62	67	53	68
65–74	42	33	38	33	47	32
Sex						
Male	52	54	52	54	52	54
Female	48	46	48	46	48	46
Race						
African-American	14	8	25	13	1	2
White	80	85	69	80	93	92
Other	6	7	6	7	6	6
Center						
Detroit	20	24	23	31	16	14
Iowa	26	27	21	22	32	34
Los Angeles	26	24	29	25	22	23
Seattle	28	24	26	22	30	28
Education						
< 12 years	11	10	10	11	11	8
12–15 years	58	62	61	62	54	61
16+ years	31	29	28	27	35	31
NHL subtype						
Diffuse		32		30		34
Follicular		24		23		26
T-Cell		6		7		5
Other/Unclassifiable		38		41		35

Table 2. Adjusted† ORs and 95% CI for NHL (all, diffuse, follicular) according to anthropometric measures, SEER-NCI study (Groups A and B), 1998–2000

Variable	Controls	All NHL cases			Diffuse NHL			Follicular NHL		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Height (inches)										
55–64	283	308	1	reference	93	1	reference	71	1	reference
65–67	259	305	1.09	0.85–1.39	93	1.04	0.73–1.49	77	1.28	0.88–1.88
68–70	213	298	1.37	1.00–1.89	94	1.23	0.78–1.92	65	1.68	1.03–2.75
71–78	232	319	1.38	0.98–1.94	112	1.39	0.86–2.24	77	2.00	1.18–3.39
			p-trend = 0.06			p-trend = 0.1			p-trend = 0.01	
Weight (pounds)										
100–150	286	318	1	reference	90	1	reference	80	1	reference
151–173	203	274	1.26	0.97–1.62	78	1.29	0.89–1.88	75	1.43	0.98–2.11
174–200	271	333	1.10	0.86–1.42	101	1.18	0.81–1.70	80	1.12	0.76–1.65
201–300	217	292	1.22	0.93–1.60	118	1.83	1.26–2.66	50	0.91	0.58–1.41
			p-trend = 0.3			p-trend = 0.003			p-trend = 0.5	
Body mass index (kg/m^2)										
15–24	305	398	1	reference	117	1	reference	104	1	reference
25–29	391	477	0.95	0.77–1.17	141	0.98	0.73–1.32	122	0.98	0.71–1.33
30–34	187	212	0.89	0.69–1.15	75	1.11	0.78–1.59	40	0.69	0.45–1.05
35–50	94	132	1.11	0.82–1.52	57	1.73	1.15–2.59	23	0.75	0.45–1.25
			p-trend = 0.9			p-trend = 0.009			p-trend = 0.08	

† Adjusted for age, gender, race, and study center.

with risk of all NHL combined. However, risk patterns differed for the two most common NHL subtypes. For diffuse NHL, we saw positive associations with both weight (OR = 1.83 for heaviest group; 95% CI 1.26–2.66; p-trend = 0.003) and BMI (OR = 1.73 for ≥35 *versus* <25 kg/m^2; 95% CI 1.15–2.59; p-trend = 0.009). In contrast, height was positively associated with risk of follicular NHL (OR = 2.00 for the tallest group; 95% CI 1.18–3.39; p-trend = 0.01), while there was no association with weight and a weak and not statistically significant inverse association with BMI.

The associations for weight and BMI were broadly similar for Group A (Table 3) and B (Table 4) participants. However, the association of height with risk of all NHL, and particularly follicular NHL, was much stronger among Group A than Group B participants. Exclusion of African-Americans from group A did not explain these differences (data not shown).

We next excluded participants whose BMI was 15–18.5 kg/m^2 from the reference group (for the full sample), and the associations reported in Table 2 were essentially unchanged (data not shown). When we evaluated BMI using the approximate quartile cutpoints based on the distribution of BMI in the control group (15–24, 25–27, 28–30, 31+ kg/m^2), the associations for all NHL combined and follicular NHL were similar to the results in Table 2, while the association with diffuse NHL was attenuated (OR = 1.45 for BMI 31+ *versus* <25 kg/m^2, 95% CI 1.04–2.02).

Medical conditions

We next evaluated the history of several medical conditions related to obesity and physical inactivity, which were only available for Group A participants (Table 3). Neither type 2 diabetes nor treatment for diabetes was associated with NHL overall, or diffuse or follicular NHL in particular. Use of insulin showed a positive association with diffuse NHL (OR = 2.23), but the 95% confidence interval lacked precision (0.85–5.84) due to the small number of respondents using insulin. History of gallstones was not associated with risk of NHL overall or with risk of follicular NHL, but was positively associated with risk of diffuse NHL (OR = 1.95; 95% CI 1.11–3.40). History of hypertension, use of calcium channel blockers, or use of diuretics was not associated with NHL risk overall or with diffuse or follicular NHL.

Total energy and physical activity

Data on total energy and physical activity (Table 4) were available for Group B participants only. Total energy was not associated with risk of all NHL combined or with follicular NHL, while we observed a weak positive association with diffuse NHL. Occupational physical activity and vigorous housework were not associated with risk of NHL. In contrast, non-occupational physical activity was inversely associated with NHL risk (p-trend = 0.04). When the components of non-occupational physical

Table 3. Adjusted[†] ORs and 95% CI for NHL (all, diffuse, follicular) according to selected diseases, SEER-NCI study (Group A participants), 1998–2000

Exposure	Controls	All NHL cases			Diffuse NHL			Follicular NHL		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Height (inches)										
55–64	172	198	1	reference	61	1	reference	42	1	reference
65–67	150	183	1.13	0.82–1.57	49	0.91	0.56–1.48	44	1.36	0.81–2.26
68–70	126	173	1.43	0.94–2.18	48	1.06	0.57–1.97	37	1.81	0.94–3.46
71–78	140	205	1.58	1.01–2.49	66	1.42	0.74–2.72	49	2.44	1.22–4.90
			p-trend = 0.04			p-trend = 0.2			p-trend = 0.02	
Weight (pounds)										
100–150	161	188	1	reference	52	1	reference	45	1	reference
151–173	118	157	1.22	0.87–1.71	41	1.21	0.72–2.01	40	1.37	0.81–2.30
174–200	160	203	1.12	0.81–1.55	57	1.14	0.70–1.86	47	1.15	0.69–1.91
201–300	141	198	1.27	0.90–1.79	69	1.73	1.05–2.86	36	1.07	0.61–1.88
			p-trend = 0.3			p-trend = 0.03			p-trend = 1.0	
Body mass index (kg/m^2)										
15–24	172	233	1	reference	64	1	reference	58	1	reference
25–29	224	280	0.93	0.71–1.23	77	1.01	0.67–1.52	69	0.96	0.63–1.47
30–34	124	155	0.92	0.67–1.27	50	1.18	0.74–1.87	31	0.79	0.47–1.31
35–50	63	84	1.04	0.70–1.53	31	1.48	0.86–2.54	13	0.66	0.34–1.31
			p-trend = 1.0			p-trend = 0.09			p-trend = 0.2	
Diabetes										
No	536	699	1	reference	203	1	reference	161	1	reference
Type 1	2	4	1.33	0.23–7.58	0			2		
Type 2	51	54	0.86	0.57–1.31	19	1.19	0.66–2.14	9	0.67	0.31–1.41
Treatment for Type 2 diabetes										
No agents	5	8	1.27	0.40–4.06	3	2.22	0.50–9.96	3	2.53	0.57–11.2
Oral only	32	26	0.63	0.36–1.09	8	0.74	0.33–1.72	4	0.46	0.16–1.35
Insulin	12	20	1.49	0.71–3.15	8	2.23	0.85–5.84	2	0.63	0.14–2.92
History of gallstones										
No	546	701	1	reference	199	1	reference	163	1	reference
Yes	43	58	1.08	0.70–1.65	25	1.95	1.11–3.40	9	0.71	0.33–1.52
Hypertension										
No	382	513	1	reference	156	1	reference	118	1	reference
Yes	207	246	0.97	0.76–1.23	68	0.93	0.65–1.33	54	0.92	0.63–1.35
Took calcium channel blocker										
No	136	159	0.96	0.73–1.27	45	0.95	0.63–1.42	34	0.88	0.57–1.38
Yes	64	82	1.06	0.73–1.54	20	0.88	0.50–1.56	19	1.08	0.60–1.94
Took diuretic										
No	115	140	0.96	0.72–1.29	39	0.91	0.59–1.39	34	1.00	0.63–1.57
Yes	89	105	1.00	0.72–1.39	29	1.00	0.61–1.63	20	0.83	0.48–1.44

[†] Adjusted for age, gender, race, and study center.

activity were evaluated separately, inverse associations were slightly stronger for vigorous compared to moderate activity. Duration of activity was inversely associated with risk, while frequency of activity showed an inverse association, except for the highest group (five or more days/week), for which the ORs were greater than one (but not statistically significant). Our data were too sparse to evaluate the effect of high levels of very frequent exercise with NHL risk. In NHL subtype analysis (Table 4), the inverse association was strongest for diffuse NHL, but the inverse association was also apparent for follicular NHL, although it was weaker and not statistically significant.

Multivariable models

Due to the data collection scheme, we were unable to simultaneously include all variables in the same model. For Group A participants, when BMI and history of gallstones were included in a multivariable model for diffuse NHL, the association for gallstones did not materially change, while the positive association with BMI slightly weakened (OR = 1.39 for BMI 35+ *versus* <25, 95% CI 0.81–2.38); associations for all NHL and follicular NHL were not materially changed. When height and history of gallstones were included in a

Table 4. Adjusted† ORs and 95% CI for NHL (all, diffuse, follicular) according to total energy and level and type of physical activity, SEER-NCI study (Group B participants), 1998–2000

Variable	Controls	All NHL cases			Diffuse NHL			Follicular NHL		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Height (inches)										
55–64	111	109	1	reference	32	1	reference	29	1	reference
65–67	109	122	1.08	0.73–1.59	44	1.37	0.79–2.38	33	1.20	0.66–2.16
68–70	86	125	1.35	0.81–2.23	45	1.54	0.78–3.04	28	1.41	0.67–3.00
71–78	91	109	1.09	0.64–1.87	44	1.42	0.68–2.94	26	1.28	0.56–2.93
			p-trend = 0.7			*p*-trend = 0.3			*p*-trend = 0.6	
Weight (pounds)										
100–150	124	128	1	reference	38	1	reference	34	1	reference
151–173	85	115	1.28	0.85–1.90	36	1.42	0.80–2.53	35	1.59	0.88–2.88
174–200	111	129	0.99	0.66–1.50	44	1.18	0.66–2.11	32	0.98	0.52–1.85
201–300	75	92	1.11	0.71–1.72	47	1.97	1.10–3.54	14	0.66	0.31–1.41
			p-trend = 1.0			*p*-trend = 0.05			*p*-trend = 0.2	
Body mass index (kg/m^2)										
15–24	132	162	1	reference	52	1	reference	44	1	reference
25–29	167	194	0.93	0.67–1.28	63	0.93	0.59–1.46	53	0.97	0.60–1.57
30–34	63	57	0.77	0.50–1.19	24	1.00	0.56–1.81	9	0.47	0.21–1.04
35–50	30	48	1.28	0.76–2.15	26	2.22	1.18–4.19	10	0.94	0.42–2.11
			p-trend = 0.9			*p*-trend = 0.05			*p*-trend = 0.3	
Total energy (kcal/day)										
< 1323	98	107	1	reference	31	1	reference	34	1	reference
1324–1646	98	79	0.68	0.45–1.04	29	0.85	0.47–1.54	20	0.56	0.29–1.06
1647–2140	98	131	1.07	0.71–1.59	49	1.32	0.75–2.31	29	0.72	0.39–1.33
> 2140	97	149	1.12	0.74–1.69	58	1.43	0.81–2.52	35	0.82	0.45–1.52
			p-trend = 0.2			*p*-trend = 0.08			*p*-trend = 0.8	
Occupational physical activity										
Does not work	206	191	0.91	0.63–1.32	62	0.97	0.58–1.62	46	0.83	0.48–1.46
Mostly Sit	98	141	1	reference	43	1	reference	42	1	reference
Mostly walk	42	42	0.72	0.43–1.20	16	0.88	0.44–1.76	10	0.65	0.29–1.44
Some exercise	42	60	0.97	0.60–1.58	29	1.47	0.79–2.72	10	0.52	0.23–1.16
Mostly exercise	26	39	0.98	0.55–1.74	17	1.32	0.63–2.76	11	1.04	0.45–2.37
Vigorous housework										
No	168	171	1	reference	65	1	reference	39	1	reference
Yes	241	286	1.23	0.92–1.63	96	1.04	0.71–1.54	77	1.41	0.90–2.21
Non-occupational physical activity (metabolic equivalents/week)										
None	59	89	1	reference	34	1	reference	22	1	reference
30–270	94	110	0.75	0.49–1.17	37	0.61	0.34–1.10	24	0.56	0.28–1.11
271–675	85	97	0.71	0.45–1.11	30	0.55	0.30–1.01	30	0.79	0.41–1.53
676–1080	87	73	0.55	0.34–0.87	28	0.52	0.28–0.96	16	0.43	0.20–0.89
> 1080	81	89	0.68	0.43–1.08	29	0.53	0.29–0.99	27	0.79	0.40–1.56
			p-trend = 0.04			*p*-trend = 0.08			*p*-trend = 0.5	
Vigorous leisure time physical activity										
No	239	286	1	reference	112	1	reference	69	1	reference
Yes	176	186	0.79	0.60–1.04	57	0.60	0.40–0.88	52	0.93	0.61–1.42
Frequency (days/week)										
1–2	52	47	0.63	0.40–0.99	6	0.18	0.08–0.45	15	0.79	0.40–1.54
3–4	83	71	0.62	0.43–0.90	21	0.45	0.26–0.78	20	0.72	0.41–1.29
5+	37	62	1.35	0.86–2.13	28	1.58	0.90–2.75	16	1.57	0.81–3.04
			p-trend = 0.7			*p*-trend = 0.7			*p*-trend = 0.8	
Duration (min/day)										
< 20	23	38	1.26	0.72–2.21	10	0.83	0.37–1.84	12	1.71	0.79–3.72
20–39	71	71	0.69	0.47–1.02	23	0.54	0.32–0.94	18	0.72	0.39–1.33
40+	80	71	0.68	0.47–0.99	21	0.51	0.30–0.88	20	0.82	0.46–1.45
			p-trend = 0.02			*p*-trend = 0.005			*p*-trend = 0.3	
Total (min/week)										
< 76 min/week	66	62	0.67	0.45–0.99	14	0.36	0.19–0.68	18	0.76	0.41–1.40
76–135 min/week	58	58	0.75	0.49–1.14	18	0.59	0.32–1.06	19	1.09	0.60–2.01
136+ min/week	47	55	0.91	0.59–1.42	20	0.84	0.47–1.51	13	0.91	0.46–1.81
			p-trend = 0.3			*p*-trend = 0.1			*p*-trend = 0.8	

Table 4. Continued

Variable	Controls	All NHL cases			Diffuse NHL			Follicular NHL		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Moderate leisure time physical activity										
No	158	194	1	reference	74	1	reference	40	1	reference
Yes	254	276	0.88	0.67–1.17	92	0.76	0.52–1.11	80	1.18	0.76–1.84
			p-trend = 0.4			p-trend = 0.2			p-trend = 0.4	
Frequency (days/week)										
1–2 d/week	57	67	0.80	0.52–1.24	22	0.69	0.38–1.25	21	1.10	0.58–2.09
3–4 d/week	118	103	0.73	0.51–1.02	33	0.60	0.37–0.97	30	0.97	0.56–1.67
5+ d/week	74	93	1.12	0.77–1.65	32	0.99	0.59–1.66	26	1.50	0.84–2.69
			p-trend = 0.8			p-trend = 0.5			p-trend = 0.3	
Duration (min/day)										
< 20 min/d	46	66	1.14	0.73–1.77	19	0.84	0.45–1.56	19	1.53	0.79–2.95
20–39 min/d	117	128	0.89	0.63–1.24	41	0.72	0.46–1.15	39	1.23	0.74–2.07
40+ min/d	87	77	0.73	0.50–1.07	30	0.75	0.45–1.25	21	0.92	0.51–1.69
			p-trend = 0.1			p-trend = 0.2			p-trend = 0.9	
Total (min/week)										
< 76 min/week	88	96	0.82	0.57–1.18	28	0.60	0.36–1.02	34	1.32	0.77–2.27
76–140 min/week	86	88	0.82	0.57–1.19	28	0.67	0.40–1.14	22	0.95	0.52–1.74
141+ min/week	72	75	0.94	0.63–1.39	29	0.94	0.56–1.60	20	1.15	0.62–2.14
			p-trend = 0.5			p-trend = 0.6			p-trend = 0.7	

† Adjusted for age, gender, race, and study center.

multivariable model, there were no material changes from the estimates reported in Table 3 (data not shown).

For group B participants, we were able to assess a wider range of potential confounding variables, including total energy, height, education, family history of lymphoma, alcohol use, and cigarette smoking; only alcohol use (which is inversely associated with NHL in this study) showed any notable confounding, particularly for physical activity. Table 5 presents the final model that included BMI, height, non-occupational physical activity, alcohol use, and the design variables. BMI remained positively associated with risk of diffuse NHL (OR = 2.05; 95% CI 1.02–4.13). The inverse associations of physical activity for NHL overall and each subtype attenuated toward the null and none of the point estimates were statistically significant. The association of height with NHL overall remained unchanged, while the associations with diffuse and follicular NHL slightly strengthened, although none of the point estimates were statistically significant.

Discussion

In this population-based case–control study, we found no association of weight, BMI, total energy intake, or related medical conditions (type 2 diabetes, gallstones, and hypertension) with risk of all NHL combined, while non-occupational physical activity was inversely associated with risk. The latter association lacked dose-response, and weakened after adjustment for BMI and (in particular) alcohol consumption. There was evidence for etiologic heterogeneity by NHL subtype for obesity-related factors. Specifically, for diffuse but not follicular NHL, there were positive associations with BMI, total energy, and history of gallstones. The association of BMI with diffuse NHL did not appear to be linear, as there was no gradient in risk for BMIs below 30 kg/m^2. The association of BMI with diffuse NHL did not appear to be confounded by age, sex, physical activity, total energy, alcohol use or other factors evaluated. History of gallstones was also positively associated with risk of diffuse NHL, and the association of BMI with diffuse NHL attenuated after adjustment for gallstones, which is consistent with gallstones being strongly associated with obesity [46]. Finally, we found some evidence for a positive association of height with risk of NHL, although there was some inconsistency in the estimate of effect between the two study groups.

Strengths of this study include the population-based design, evaluation of multiple facets of energy balance including anthropometrics, diet, physical activity, and related medical conditions, and the evaluation of associations for the two most common NHL subtypes. There are also limitations. The response rates for cases,

Table 5. Adjusted[†] ORs and 95% CI for non-occupational physical activity and BMI for NHL (all, diffuse, follicular), SEER-NCI study (Group B participants), 1998–2000

	All NHL cases		Diffuse NHL		Follicular NHL	
	OR	95% CI	OR	95% CI	OR	95% CI
Height (inches)						
55–64	1	reference	1	reference	1	reference
65–67	1.13	0.74–1.73	1.45	0.79–2.66	1.28	0.67–2.44
68–70	1.23	0.71–2.11	1.62	0.77–3.39	1.36	0.60–3.07
71–78	1.10	0.62–1.95	1.63	0.75–3.57	1.36	0.56–3.32
	p-trend = 0.8		p-trend = 0.2		p-trend = 0.7	
Body mass index (kg/m^2)						
15–24	1	reference	1	reference	1	reference
25–29	0.95	0.67–1.33	1.01	0.62–1.64	1.10	0.65–1.86
30–34	0.77	0.48–1.23	0.99	0.52–1.88	0.46	0.19–1.08
35–50	1.12	0.64–1.98	2.05	1.02–4.13	0.85	0.35–2.08
	p-trend = 0.8		p-trend = 0.1		p-trend = 0.4	
Non-occupational physical activity (metabolic equivalents/week)						
None	1	reference	1	reference	1	reference
30–270	0.80	0.50–1.28	0.76	0.40–1.45	0.51	0.24–1.08
271–675	0.82	0.50–1.33	0.72	0.37–1.40	0.80	0.38–1.65
676–1080	0.70	0.42–1.17	0.78	0.39–1.57	0.43	0.18–1.01
> 1080	0.83	0.50–1.38	0.82	0.41–1.66	0.85	0.39–1.83
	p-trend = 0.5		p-trend = 0.9		p-trend = 1.0	

[†] Simultaneously adjusted for each variable as well as age, gender, race, study center, and alcohol use.

and in particular controls, were relatively low, although they were in the range of many of the current generation of population-based case–control studies with in-home interviews. The impact of these low response rates on our results, however, is not easy to evaluate. The major associations found in this study did hold in subgroups defined by age, sex, race, study center and educational level, which had varying response rates.

Another limitation is the potential for both differential and non-differential recall bias with respect to the exposures evaluated. Anthropometrics were self-reported during an in-home interview, and have reasonable validity [47]. Diet was self-reported using a self-administered food frequency questionnaire that has been shown to be valid and reliable in similar populations [41]. Assessment of physical activity was limited and was not validated, but is similar to other short assessments used in epidemiologic studies [48] and included data on the main parameters of frequency, duration and intensity for assessing physical activity [49]. Self-reported major medical conditions were not validated, although these exposures appear to be reported with reasonable validity [50, 51]. Differential recall bias could have affected our results (magnitude and direction difficult to predict), although for these exposures it seems more likely that non-differential recall bias would have a greater impact, and would be expected to attenuate associations. Measurement error could have also had a differential impact on our results. For example, measurement error was likely to be much higher for the more complex construct of physical activity relative to obesity as measured by BMI, making it more difficult to detect associations with the former variable.

For this analysis, we relied on the SEER-reported subtype diagnosis for diffuse and follicular NHL without central review, although this would be expected to introduce relatively little error given the high concordance with expert review for these specific subtypes [52–54]. Response rates differed between follicular and diffuse NHL, and this was mainly due to greater early mortality among diffuse cases. While this could potentially introduce a bias in the association of obesity with diffuse NHL, the modest difference in response rates (16%) and the lack of such a differential for physical activity suggests that this was not a major source of bias. Also, there was no evidence for this type of bias in cohort study which evaluated the role of early mortality in the association of obesity with NHL [17].

While the split sample study design allowed for more extensive data collection, it also made it more difficult to interpret the unexpected differences between groups for the association of height with NHL, and also complicated multivariable modeling. Finally, even with this modestly sized study, we were underpowered for rare exposures, evaluation of interactions, and assessment of associations with rare NHL subtypes.

Our finding of no association of BMI with risk of all NHL combined is consistent with five [14–18] of six [9]

incidence studies and one [12] of two [10] mortality studies. A population-based case–control study from Sweden [19] and a hospital-based case–control study from Italy [13] reported no association of BMI with all NHL combined, while two [8,11] population-based case-control studies from North America reported positive associations. Of the positive studies, increased risk has ranged from 30% to 200%, but has mainly occurred when BMIs exceed 30 kg/m^2, and only one study has shown a dose-response across the entire range of BMIs [8]. We found no evidence for effect modification by sex. One study reported that the association of obesity with NHL was specific to women [9], while all other positive studies reported only slightly stronger associations among women [8, 10] or no sex differences [11]. Our finding of a specific association of high BMI with risk of diffuse but not follicular NHL replicates the finding of Chang *et al*. [19], who reported persons with a BMI of $\geq$27.6 kg/m^2 were a 40% greater risk of diffuse NHL compared to persons with a BMI of $<$22.8 kg/m^2 (95% CI 1.1–1.7). Of two other studies that assessed subtype-specific associations, one found no association for either of these subtypes [17], and the other found positive associations for both of these subtypes [20]. BMI does have limitations as a measurement of obesity as it does not distinguish fat *versus* lean mass, or body fat distribution [6]; there are few data on these measures for NHL, although body fat distribution was not associated with risk of NHL among older women [17].

We found some evidence for an association of height with risk of NHL, and this was stronger among Group A participants. However, there was a positive association among Group B participants (although not statistically significant), and this association did not appear to be confounded by physical activity, BMI or alcohol use. Epidemiologic data on height and risk of NHL are limited, with two incidence studies reporting no association [15, 17], while one incidence [16] and one mortality [35] study reported positive associations.

Our data also provide some support for an inverse association of non-occupational physical activity with risk of NHL. Leisure time physical activity was not associated with NHL incidence in a cohort of older women, although there was suggestive evidence of an inverse association for follicular NHL [17]. Occupational physical activity was not associated with risk in this study, consistent with two previous studies [55, 56]. Athletic participation in college was not associated with risk of NHL [57, 58]. The limited support in this study for a beneficial effect of physical activity on NHL risk suggests that further evaluation with more detailed exposure assessment would be helpful to clarify the issue.

Our finding of no association of adult-onset diabetes with risk of NHL is consistent with four case–control studies [30–32] and three SIR (standardized incidence ratio) studies [27, 29, 33]. In contrast, two case–control [22, 23], three SIR [21, 24, 26] and two cohort studies [25, 28] reported an increased risk of adult-onset diabetes with NHL. Our assessment of diabetes was limited to self-reported ever diagnosis and age at diagnosis, although this was similar to many of these other studies [22, 23, 25, 28, 30–32] and the prevalence of type 2 diabetes in our control group is consistent with national data [59]; however, under-diagnosis of this condition is a limitation.

Our finding of a positive association of history of gallstones with risk of diffuse NHL has, to our knowledge, not been previously reported. The pathogenesis of gallstones is thought to be closely linked to metabolic abnormalities related to obesity, which is a strong risk factor for the disease [46]. Thus, our finding was consistent with a role of obesity in diffuse NHL and gallstones are most likely a downstream marker of long-standing obesity, although there may be other shared etiologies which we were not able to address in this study.

Hypertension and its treatment have been suggested as risk factors for cancer, although data on NHL are sparse [60]. History of hypertension and diuretic use were not associated with NHL risk, consistent with limited prior data [23,30]. Our evaluation of use of calcium channel blockers and risk of NHL was prompted by a positive association between use of these agents and risk of hematopoietic cancer (RR = 2.57; 95% CI 1.13–5.83) [61], but we found no evidence to support this association.

The association of obesity with NHL remains tentative. The major mechanistic hypotheses linking obesity to cancer include effects on endogenous hormone metabolism; insulin and insulin-like growth factors leading to a state of hyperinsulinemia; increased endogenous production of reactive oxygen species leading to DNA damage; alteration of the immune response through leptin and related factors; and increased inflammatory response, particularly through TNF-alpha and IL–6 [6, 62]. All these could be plausibly related to the etiology of NHL, given the potential implication of these factors in lymphomagenesis [63]. The specificity of the association with diffuse NHL is also intriguing as genetic polymorphisms related to higher TNF-alpha production have been associated with diffuse but not follicular NHL (Rothman *et al*. (Submitted)). These mechanisms may also explain increased cancer risk persons among persons with diabetes and the protective effect of physical activity. The suggestive

positive association with height raises the hypothesis that nutrition in early life may also play a role in the etiology of NHL [34]. More specific hypotheses, perhaps tested by incorporating genetic and serologic biomarkers, will be needed to understand the mechanistic basis of any association, while mindful of the inter-related nature of these pathways. Finally, our results raise the possibility that the etiology of diffuse NHL may be related in part to the physiologic abnormalities related to obesity, but that this is less likely for the etiology of follicular NHL.

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